MMHCC
the Mouse Models of Human Cancers Consortium

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Discoveries about Human Tumors using Gene Expression Profiling of Mouse Cancer Models

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In a recent publication in *Nature Genetics*, Thomas Graeber and Charles Sawyers (1) summarized several publications that illustrate the emerging value of cross-species comparisons of gene expression profiles for human clinical science. They also proposed a comprehensive approach to wider application of human/mouse comparisons that has the potential to identify clinically relevant targets for novel therapies and to define which patients have the appropriate expression profile for a given targeted therapy.

Their proposal is based on three recent publications that they cite. One is from the Sawyers laboratory (2), in which they performed gene expression profiling of a mouse cancer model based on over-expression of the human c-*Myc* oncogene specifically in the mouse prostate. The model design was prompted by the fact that the copy number of the c-*Myc* gene is often increased in human prostate cancer. To vary the dosage of c-Myc expression, they used either a probasin-*Myc* or an AAR_2-probasin-*Myc* transgene to generate founder lines that they designated as Lo-*Myc* (probasin-driven) or Hi-*Myc* (AAR_2-probasin-driven) based on the amount of transgene expression. Their publication details the histopathology properties of the various founder lines; all of the mice developed mouse prostatic intraepithelial neoplasia (mPIN) that subsequently progressed to invasive carcinoma.

Because the kinetics and penetrance of the cancer phenotype are very reliable, they performed microarray expression profiling to define a *Myc* prostate cancer profile of the molecular events that cooperate with *Myc* to drive prostate cancer progression. They isolated mPIN and tumors from all four prostate lobes of the Hi-*Myc* animals for microarray and CGH analysis. One change of particular interest was variation in levels of a putative human prostate tumor suppressor gene, called *NKX3.1*, in mPIN lesions; expression of this gene was not detected in any samples of invasive cancers. The c-*Myc* oncogene is already expressed at the mPIN stage; thus they concluded that gain of *Myc* expression coupled with loss of *NKX3.1* may be critical cooperating events when prostate cancer progresses from mPIN to invasive cancer.

Although there are some challenges to cross-species comparison of expression profiles at this time – different profiling platforms and limited representation of orthologs on human and mouse arrays – they did find that genes that correlate with *Myc* status in mouse tumors can define a "*Myc*-like" signature in human tumors. The observations about one gene in particular, *Pim-1*, are highly consistent with the present knowledge about the role of *Myc* in cancer; increased *Pim-1* expression is observed in one subset of human prostate cancer and correlates with poor outcome. From the extensive data analysis as detailed in this publication, the authors conclude that cross-species profiling comparisons can help to prioritize the usually long lists of human genes for evaluation of their function in cancer, and to enlarge the lists of genes that correlate with a specific molecular lesion across cancers from multiple tissues.

The second publication cited by Graeber and Sawyers is from the laboratory of Snorri Thorgeirsson (3). In it, the authors used global gene expression patterns from hepatocellular carcinomas (HCC) from 7 different mouse cancer models of HCC and compared them to profiles of human HCCs that had already been grouped into two subclasses, based on clinical outcome. The mouse model panel consisted of two models that are chemically induced, an *acox-1* null mouse, and four models with targeted, over-expressed transgenes (c-*Myc*; E2f1; c-*Myc* and E2f1; c-*Myc* and Tgf-alpha). Analysis of the expression patterns using hierarchical clustering segregated the models into three distinct groups. HCCs from the *acox-1* null mice and from mice whose tumors were induced with ciprofibrate (a synthetic peroxisome proliferator that is a non-genotoxic hepatocarcinogen) formed one cluster, which did not correspond to either of the two human patterns.

The gene expression pattern that distinguishes human HCCs with a poor prognosis was best represented by tumors from the c-*Myc*/Tgf-alpha transgenic mice and from mice whose tumors are induced by diethylnitrosamine, a genotoxic chemical carcinogen. They conclude that these tumors undergo extensive chromosomal damage during tumor development and progression. The third group of mice – whose tumors are induced by c-*Myc*, E2f1, or both – have expression profiles that correspond most closely to human HCCs with better prognosis. They have a somewhat higher frequency of mutations, and nuclear localization, of beta-catenin, and have lower levels of genomic instability.

These authors conclude from their study that the use of comparative functional genomics will enable researchers to distinguish from among mouse cancer models those whose molecular pathology is most closely aligned with that of human cancers. This will enhance confidence in the use of mouse models to inform the molecular pathogenesis, treatment, and prevention of human cancers.

The final publication cited by Graeber and Sawyers describes research from the laboratory of Tyler Jacks (4). The goal of this study was to compare a mouse lung cancer model that was generated by targeted expression of the K-*ras2* oncogene, implicated in the etiology of human lung cancer, with human lung cancer using expression profiling. The K-*ras2* oncogene is activated sporadically in mouse lungs through homologous recombination, and all of the mice develop lung cancer. Many of the morphology characteristics of human lung adenocarcinoma are observed in this model; however, the extent to which these features reflect the underlying molecular pathology had not previously been explored. They began by profiling tumors and normal tissue from the mice, and found that they could easily distinguish normal tissues from tumor specimens. They selected two sets of mouse genes, one set containing genes that were up-regulated in tumors, and the other, those down-regulated in tumors relative to normal lung expression. These two sets of genes were then compared to previously published human lung cancer datasets. By matching probes on human and mouse microarrays, they were able to classify the human specimens as either tumor or normal with either the up-regulated or down-regulated sets of mouse genes.

Using two methods, one termed Gene Set Enrichment Analysis (GSEA), a technique that allows the comparative analysis of the two mouse gene sets over multiple human gene sets, and the Neighborhood Mantel (NM) procedure, that permits correlation of the same gene set in the corresponding (human or mouse) data set, they were able to extract information that was not readily apparent from analysis of either mouse or human data alone. Their analysis demonstrated that the tumors in the K-*ras* sporadic mouse model more closely resemble human lung adenocarcinoma that any other tumor type to which the data were compared, and they could define a subset of up-regulated genes in both human and mouse adenocarcinoma.

Beyond using expression analysis to validate the mouse phenotype with respect to human cancer, the Jacks group also investigated whether a cross-species comparison could reveal a common signature for K-*ras*–induced lung cancer that would not be evident from inspection of either species alone. Using GSEA, they discovered that the mouse up-regulated gene set was enriched in K-*RAS2* adenocarcinomas from two large human datasets. This gene set has 89 members, and none of the individual genes is a statistically significant indicator; only by considering the genes as a set does the analysis achieve statistical significance. These authors conclude that, not only were they able to illustrate the validity of the mouse cancer model for study of the human cancer it is intended to represent, but they were also able to use a cross-species comparison to extract information of clinical relevance that otherwise would be missed.

Graeber and Sawyers use the results from these research reports to suggest that it would be valuable to move from a few informative reports of this kind to a comprehensively planned examination of perturbations of the major cancer signal pathways in a variety of tissue types in cancer models. The resulting store of mouse data, including the effects of agents that target the pathways and variation in genetic background, could sustain an in-depth program of cross-species discovery using comparable human data sets. The availability of comprehensive data would doubtless allow exploration of new hypotheses about the natural history and clinical course of cancer, and generation of new computational models of pathway interactions during the evolution of cancer. The results could fuel the identification of more effective therapy targets and parameters for disease diagnosis and prognosis.

References:

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   Cancer Cell. 2003 Sep;4(3):223-38.
3. Lee JS, Chu IS, Mikaelyan A, Calvisi DF, Heo J, Reddy JK, Thorgeirsson SS
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MouseLine

Please stop by the exhibit booth of the Mouse Models of Human Cancers Consortium (MMHCC) at the meeting of the American Association of Cancer Research (AACR) in Anaheim, California. Our booth number is 874 – come meet us in person!

Selected Meetings

May 24 - 26, 2005
Realizing the Promises: Early Detection of Cancer
Palo Alto, CA
Meeting information: http://www.canaryfund.org

June 19 - 22, 2005
8th Cancer Research UK - Beatson International Cancer Conference
Glasgow, Scotland
Meeting Information: http://www.beatson.gla.ac.uk/conf

June 22-26, 2005
Third International Symposium of Molecular Biology of Breast Cancer
Molde, Norway
Meeting information: http://www.mbbc.no

July 17 - 29, 2005
46th Annual Short Course on Medical and Experimental Mammalian Genetics
Bar Harbor, Maine
Course information: http://www.jax.org/courses/events/coursedetails.do?id=120

August 7 - 14, 2005
4th Annual Workshop On The Pathology Of Mouse Models For Human Disease
West Lafayette, Indiana
Meeting information: http://www.jax.org/courses/events/coursedetails.do?id=122

For more meetings and meeting information see
http://emice.nci.nih.gov/emice/communication/calendar/index.html

Funding Opportunities

Preclinical Study of Efficacy in Animal Models of Type 1 Diabetes
NOT-DK-05-009
National Institute of Diabetes and Digestive and Kidney Diseases
http://grants.nih.gov/grants/guide/notice-files/NOT-DK-05-009.html

Preclinical Study of Efficacy in Animal Models of Diabetic Complications
NOT-DK-05-008
National Institute of Diabetes and Digestive and Kidney Diseases
http://grants.nih.gov/grants/guide/notice-files/NOT-DK-05-008.html

Lung Response to Inhaled Highly Toxic Chemicals
PA-05-058
National Heart, Lung, and Blood Institute
National Institute of Environmental Health Sciences
http://grants.nih.gov/grants/guide/pa-files/PA-05-058.html

***In Utero* Exposure to Bioactive Food Components and Mammary Cancer Risk**
PA-05-059
National Cancer Institute
National Institute of Environmental Health Sciences
Office of Dietary Supplements
http://grants.nih.gov/grants/guide/pa-files/PA-05-059.html

June Northwest Association for Biomedical Research Regional IACUC Conference
NOT-OD-05-036
National Institutes of Health
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-036.html